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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/454,737	12/06/99	PERRICAUDET M	8076.85USC1

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	7

DATE MAILED: 03/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/454,737	Perricaudet et al.
Examiner	**Group Art Unit**
David Guzo	1636

☒ Responsive to communication(s) filed on *Dec 6, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *10-16* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenfeld et al.

Applicants claim a composition comprising a non-replicative viral vector wherein said viral vector comprises a polynucleotide sequence under the control of a promoter recognized by polymerases of muscle cells and wherein the polypeptide is expressed in said muscle cells and a pharmaceutically acceptable carrier.

Rosenfeld et al. (Science, Vol. 252, 4/19/91, pp. 431-434, see whole article, particularly Fig. 1 and Fig. 3) recites a composition comprising a non-replicative adenoviral vector wherein said viral vector comprises a polynucleotide sequence under the control of a promoter (adenoviral major late promoter) recognized by polymerases of muscle cells and wherein the polypeptide would be expressed in muscle cells and a pharmaceutically acceptable carrier. Therefore, Rosenfeld et al. teaches the claimed invention.

It is noted that intended use language (i.e. for treatment of muscular diseases) in compound or composition claims carries no patentable weight.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering (intravenously or intraarterially), to muscle cells, non-replicative recombinant adenoviral vectors with a heterologous gene inserted in the E1 region of said vector and compositions comprising said recombinant adenovirus vectors, does not reasonably provide enablement for a method of delivering any non replicative recombinant viral vector or any composition comprising said viral vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants claim a method for delivering to human and animal muscle tissue a non-replicative recombinant viral vector containing a gene encoding a polypeptide (i.e. dystrophin), said gene being under control of a promoter recognized by polymerases in muscle cells, said method comprising intravenous or intraarterial injection of said vector and compositions comprising said vectors in a pharmaceutically acceptable carrier.

The test of enablement is whether one skilled in the art could make and use the claimed

invention from the disclosures in the application coupled with information known in the art without undue experimentation (See *United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Unpredictability of the art. The art in this case involves delivery of recombinant viral vectors to specific tissues in humans or animals wherein said vectors can express a selected polypeptide in muscle cells. This art is extremely unpredictable in that the ability to deliver recombinant viral vectors to target tissues and the ability of viral vectors to express genes of interest in selected tissues *in vivo* is problematic (See Orkin et al., Verma et al. and Anderson for reviews). Indeed, Verma et al. notes that "The Achilles heel of gene therapy is gene delivery..." Verma et al. P. 239, right column).

With regard to the composition claims, the generation of recombinant viral vectors, was as of the filing date of the priority document, unpredictable. Applicants disclosure of a single adenoviral vector construct in no way enables the skilled artisan to practice the claimed invention with regard to retroviral vectors, adeno-associated viral vectors, etc. The construction of recombinant viral vectors for gene expression *in vivo* often involves extensive trial and error experimentation in order to choose the proper expression regulatory sequences for expression of

the foreign gene in the target tissues, etc. (See Verma et al., p. 240 and Kmiec, American Scientist, Vol. 87, 1999, pp. 240-247).

2) State of the art. The art, with regard to construction of and delivery of gene therapy viral vectors, is still in it's infancy as noted by Verma et al. and Anderson with no demonstrated unambiguous successes attributable to gene therapy.

3) Amount of guidance presented by applicants. Applicants present guidance only with regard to a method of delivering recombinant replication-defective adenoviral vectors with a foreign gene inserted in the deleted E1 region and provide no teachings on the construction of and delivery of any other types of viral vectors. Since the teachings on construction and use of other viral vectors are essential for practicing of the claimed invention, said teachings must be present in the specification and applicants cannot rely on knowledge of those of skill in the art to supplement the specification (See *Genentech Inc. v. Novo Nordisk A/S,* 42 USPQ2d 1001, 1997).

4) Number of working examples. Applicants only present an example of a recombinant replication defective adenoviral vector with a foreign gene inserted in the E1 region.

5) Scope of the claims. The claims are extremely broad and read on any recombinant replication defective viral vector (i.e. AAV vectors, herpesviral vectors, papillomaviral vectors, etc.) and use of said vectors to deliver genes of interest to muscle cells in any animal.

6) Nature of the invention. The invention involves delivery of recombinant viral vectors to muscle tissue in humans or animals. The nature of this invention involves delivery of gene therapy

vectors and as noted by Verma et al. and Anderson, delivery of viral vectors to target tissues *in vivo* is extremely problematic.

7) Level of skill in the art. The level of skill in this art is high; however, as noted by Verma et al. and Anderson, those of highest skill in the art have yet to overcome hurdles to successful viral vector mediated gene delivery to target tissues *in vivo*.

Given the above analysis of the factors which the courts have indicated are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

7. Claims 15-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is based upon a reading of the intended use language (for treatment of muscular diseases) into the claims.

Applicants claim a composition for treatment of muscular diseases comprising a non-replicative recombinant viral vector wherein the viral vector expresses a heterologous gene under control of a promoter recognized by polymerases of muscle cells. An analysis of the *Wands*

factors follows:

1) Unpredictability of the art. The gene therapy art is extremely unpredictable. This unpredictability is manifested at almost every level of the art. As noted by Verma et al. and Anderson et al., gene delivery to target organs and reliable gene expression *in vivo* are extremely unpredictable. Indeed, even as late as February 2000 (See Fox, Nature Biotechnology, Vol. 18, 18 Feb. 2000, pp. 143-144), use of recombinant adenoviral vectors for gene therapy is fraught with unpredictability. Fox notes that the latest results from use of adenoviral vectors for gene therapy reveals unpredictability with regard to the the dosages of the vectors. Specifically, Fox notes that "...the doses at which there are toxic effects or potential therapeutic effects may be separated only narrowly, and there may be thresholds where adverse effects abruptly appear—complicating how vectors might be used and perhaps undermining the reliability of results from tests in animals." (Fox, p. 144) and that problems associated with adverse immunological effects in patients and reliable delivery of the vectors to the target tissues make the use of these vectors problematic.

2) State of the art. As noted by Verma et al. and Anderson, no gene therapy protocol has been unambiguously demonstrated to be successful. The art at the time of applicants' invention was at it's infancy.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance presented by applicants. Applicants provide no guidance on the actual treatment of any muscular diseases in humans or animals. Applicants provide no guidance on how the skilled artisan would overcome the art recognized hurdles to successful practicing of gene therapy (i.e. obtaining reliable long term expression of transgenes in human tissues, avoiding adverse immunological responses to the vectors, obtaining reliable and selective distribution of the vectors to the appropriate target tissues in humans, etc.

5) Scope of the invention. The scope of the invention is broad and encompasses any recombinant non-replicative viral vectors and use of said vectors for treatment of any muscle disease.

6) Level of skill in the art. The level of skill in the gene therapy art is high. However, as noted by some of the foremost experts in gene therapy (See Anderson, Verma et al., etc.), significant hurdles need to be overcome to enable the successful practicing of gene therapy.

7) Nature of the invention. The invention involves one of the most complex areas of molecular biology/medicine; the field of gene therapy.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 16 are vague in the recitation of the phrase "...for treatment of muscular diseases..." since intended use language in compound or composition claims carries no patentable weight and should be deleted from the claims because it implies a method for accomplishing some outcome without presenting any method steps.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for the organization

where this application or proceeding is assigned is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVID GUZO
PRIMARY EXAMINER

David Guzo
March 10, 2000